European Review for Medical and Pharmacological Sciences 2019; 23: 1322-1334

Role of phase angle in the evaluation of effect of an immuno-enhanced formula in post-surgical cancer patients: a randomized clinical trial

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Abstract. – OBJECTIVE: Neoplastic disease is frequently associated with poor nutritional status or severe malnutrition. Diet and nutritional intervention are becoming increasingly important for prognosis and quality of life in cancer patients. Accessible and repeatable tools for assessing nutritional status with body composition techniques seems to be fundamental. The aim of this study was to evaluate the effects of immunonutrition on body composition parameters, inflammatory response and nutritional status in patients at stage III of head and neck squamous carcinoma (HNSCC).

PATIENTS AND METHODS: In our work, 50 malnourished subjects with HNSCC staging III were recruited and treated with oral diet (OD) or enteral nutrition (EN). Patient under EN followed, for the first three days, enteral standard nutrition (ESN) and then enteral immunonutrition (EIN). Nutrition state was evaluated on days 0, 3, and 8 through body composition and biochemical analyses.

RESULTS: After 8 days, the EIN treatment showed a significant improvement in phase angle, pre-albumin, retinol binding protein and transferrin compared to the OD treatment.

CONCLUSIONS: Our results showed that immunonutrition treatment improves the nutritional status of neoplastic patients, supporting chemotherapy. The phase angle is not only a predictor of cancer survival, but has also proved to be useful in the surveillance of nutritional status improvement as well as biochemical indices.

Key Words
Immunonutrition, Bioelectrical impedance analysis, Phase angle, Cachexia, Cancer.

Abbreviations

Bioelectrical Impedance Analysis (BIA), Enteral Immunonutrition (EIN), Enteral Nutrition (EN), Enteral Nutrition Treatment (ESN), Head and Neck Cancer (HNC), Head and Neck Squamous Cell Carcinoma (HNSCC), Human Papillomavirus (HPV), Medium Chain Triglycerides (MCT), Monounsaturated Fatty Acids (MUFA), Oral Diet (OD), Percutaneous Endoscopic Gastrostomy (PEG), Phase Angle (PA), Radiochemotherapy (RCT), Tumor Necrosis Factor-alpha (TNF-α).

Introduction

Cancer is the second leading cause of death worldwide and it is in constant growing. In Italy, approximately 250,000 cancers per year are diagnosed and cancer survival rates are in line with the European average. The 50% of women in the 5 years after the first cancer diagnosis are affected by less severe types of cancer (breast, colorectal, cervical, and uterine body), against the most lethal tumors usually affecting men (lung, colon-rectum, stomach)[1].

Both in the United States and Europe, patients with metastatic cancer have a scarce chance of recovery, and the mortality rate remains high with a 5-year survival rate of around 40%[2]. However, with a precise, personalized and integrated multidisciplinary treatment, it is possible, in relatively frequent cases, to chronicle the disease

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and control the related symptoms for prolonged periods. Besides survival, we must take into account the quality of life. This underlines how a treatment, to be considered effective, should make the cancer patient live longer and in an acceptable condition.

The lack of ability to control the symptoms associated with the anticancer therapy and the disease itself can lead the patient to not continue with perseverance a potentially useful treatment. The interruption of anticancer therapy may also depend on the worsening of nutritional state, associated with the several side effects, such as asthenia, pain, dyspnea, anorexia, cachexia, diarrhea, constipation, mucositis, nausea, and vomiting. Poor nutritional health can lead to a decrease in loco-regional control of cancer and a subsequent overall patient survival reduction[3]. On the other hand, cancer disease has a very negative impact on nutritional status. From a pathogenic point of view, the tumor can cause a reduction in food intake either directly, mechanically interfering with the digestive tract, or indirectly, producing inhibitory substances that can act on both peripheral and hypothalamic receptors. More than 80% of neoplastic patients lose body weight, and 20-30% of these patients die from malnutrition and not for cancer. Frequency and severity of weight loss, associated with cancer, vary depending on the type of neoplasia. For example, weight loss occurs in 72% of pancreatic neoplasms, 69% of esophageal neoplasms, 67% of gastric neoplasms, 57% of head and neck cancers, 34% of colorectal neoplasms, and in 31% of cases of non-Hodgkin's lymphoma[4]. Therefore, the neoplastic disease is the clinical condition that is most frequently associated with the concept of severe malnutrition, up to cachexia. Cachexia, in oncology, is described as a multifactorial syndrome, characterized by the gradual loss of muscle mass, which may or may not necessarily be accompanied by a weight loss greater than 10%, fat mass loss, systemic inflammation, reduced food intake and increased susceptibility to infections[5]. In general, weight loss affects 30 to 80% of patients with cancer, and it is severe in more than 10%, in 15% of cases. The progressive depletion of skeletal muscle tissue causes asthenia, reduced physical function, progressive disability with a consequent reduction in quality of life, and the increase in morbidity and mortality[6]. The loss of muscle mass can also drastically reduce the responsiveness of the tumor to chemo and radiotherapy and lead to greater intolerance to treatments[5].

Given the relevance of nutrition in oncology patients' prognosis and quality of life, the assessment of nutritional status through body composition techniques seems to be fundamental[7]. Bioelectrical impedance analysis (BIA) is a safe, rapid and noninvasive tool to assess nutritional status and prognosis. In oncology, BIA is used to determine nutritional conditions, fluid deficits[8], clinical outcome and quality of life. More specifically, phase angle (PA) is one of the best predictive clinical factor[9] and values below the fifth reference percentile are associated to a decreased muscle strength, impaired quality of life and increased mortality in cancer patients[10].

It is, therefore, necessary that oncologists do not only limit themselves to considering the nutritional symptoms of the cancer patients, but also pay attention to the metabolic-nutritional aspects at the time of the diagnosis of cancer, preventing the onset of symptoms. In fact, the result of antitumor therapy is closely related to the effectiveness of supportive therapies, in particular nutritional, that have the primary purpose of preventing, controlling or alleviating the complications and side effects of chemotherapy, therefore improving the quality of life of patients with cancer. In a retrospective study, a significant reduction of interruptions of radiochemotherapy (RCT) in patients with head and neck cancer due to toxicities has been obtained with percutaneous endoscopic gastrostomy (PEG) inserted before the beginning of RCT, highlighting the importance of a prophylactic nutritional approach[11].

Among the nutritional treatments, immunonutrition in the pre or perioperative period, significantly reduced the length of hospital stay and postoperative infectious complications[12-14].

Among the most common tumors in the world, head and neck squamous cell carcinoma (HNSCC) represent about 6% of all cases, with an incidence that has been increasing over the last decades. In head and neck cancer, nutritional status could change according to the location of tumor onset. For example, patients with larynx or oral cavity cancer could be mildly or severely malnourished than pharynx; however, the nutritional status could be more affected in advanced cancer stages[15], as well as the inflammatory, angiogenic and oxidative status, which can worsen especially in stage III or IV HNSCC patients[2].

Machon et al[16] highlighted that nutritional support improved inflammation and could prevent severe acute mucositis. Therefore, the first aim of the present work was to evaluate the effects

of immune-enhanced formula containing amino acids, ω-3 fatty acids, ribonucleic acids, vitamins and antioxidants, able to modulate inflammatory response[17-19] on body composition parameters measured by BIA, and biochemical parameters in patients at stage III head and neck carcinoma. Moreover, the secondary aim of the study was to verify the possibility to use PA as a predictor of the nutritional outcome of immunonutrition treatment and prognosis in cancer patients.

Patients and Methods

Study Design

The study protocol was conducted between May 2014 and March 2018 using an interventional clinical trial. During the study protocol, 726 subjects with head-neck cancer were visited. For this work, 129 subjects with head-neck cancer were recruited at the Clinical Nutrition and Nutrigenomic Section at the University of Rome Tor Vergata. To be included in the study, all subjects had to respect the following eligibility criteria: age between 18 and 80 years old; moderate or severe malnutrition (i.e., albumin <3.5 g/dL; prealbumin <17 mg/L; transferrin <210 mg/dL; retinol binding protein <3 g/dL); HNSCC TNM staging III (HNSCC with parapharyngeal extension, and/or which involves bony structures of skull base and/or paranasal sinuses stage or tumor with intracranial extension, and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space), without lymph node metastasis (N0) and/or distant metastatic lesions (M0).

At the same time, exclusion criteria were the following: presence of metastasis and/or other cancers, active tobacco smoking, past or active cardiovascular, hepatic, metabolic, and autoimmune. Trained nutritionists and medical doctors performed patient enrollment, randomization, and allocation to interventions. The clinical trial was conducted as shown in Figure 1.

Subjects who were not able to follow per-os diet were assigned to enteral nutrition. The nutritional status assessment was performed at the Clinical Nutrition and Nutrigenomic Section, Department of Biomedicine and Prevention of University of Rome Tor Vergata. Clinicians assessed any adverse effect of the interventions by going through a checklist of symptoms that were possibly associated with the interventions. No abnormality presented during the study period. All participants, in accordance with the principles of the Declaration of Helsinki, signed a statement of informed consent. Trial Registration: This protocol has been registered with ClinicalTrials.gov Id: NCT01890070.

Nutritional Treatments

After the recruitment, subjects were divided into two groups. The first group followed the Oral Diet (OD) and the second group followed the Enteral Nutrition (EN) treatment. Subjects of the OD group followed their diet consecutively for 8 days. On the other hand, subjects of the EN group followed for the first 3 days a standard enteral nutrition treatment (ESN; Novasource Start, Nestlè®, Lausanne, Switzerland), and from the 4th day until the 8th day the enteral nutrition with immunonutrition supplements (EIN; Impact Enteral, Nestlè ®, Lausanne, Switzerland).

OD consisted of an allergen-free diet, with the following nutritional characteristics: 2448.45 kcal/day, 50% of carbohydrates, 17% proteins, 33% fats (on total Kcal: saturated fat <15%, 3% unsaturated fatty acids, 16% of monounsaturated fatty acids (MUFA); 0.8-1 g omega-3) and 32-35 g of fiber (Table I).

2000 ml of the ESN were daily administered, and the characteristics were the following: 1500 kcal/day, 43% of carbohydrates, 27% proteins, 30% fats (on total Kcal: saturated fat <17%, 8% polyunsaturated fatty acids, 5% of MUFA, 14 g of fiber and 286 mOsm/l osmolality (Table I).

The EIN consisted in an enteral formulation enriched with immunonutrients. 1500 ml of EIN were daily administered, with the following immunonutrients content: 9.15 g of medium chain triglycerides (MCT), 5 g omega-3, 19.5 g of Arginine, 1.95 g of nucleotides and 405 mg of choline. EIN nutritional characteristics were the following: 1500 kcal/day, 53% of carbohydrates, 22% proteins, 25% fats (on total Kcal: saturated fat <15%, 5% polyunsaturated fatty acids, 5% of MUFA; 5 g omega-3), <3 g of fiber and 298 mOsm/l osmolality (Table I).

Bioclinical Analyses

Blood samples were collected after a 12-hour overnight fast in sterile tubes containing EDTA (Vacutainer®) and plasma was centrifuged (1600 rpm, at 4°C for 10 min), removed, aliquot and stored at -80°C. All clinical chemistry analyses, except plasma glucose and serum lipid analysis were carried out using an ADVIA®1800 Chemistry System (Siemens Healthcare) following standard procedures.

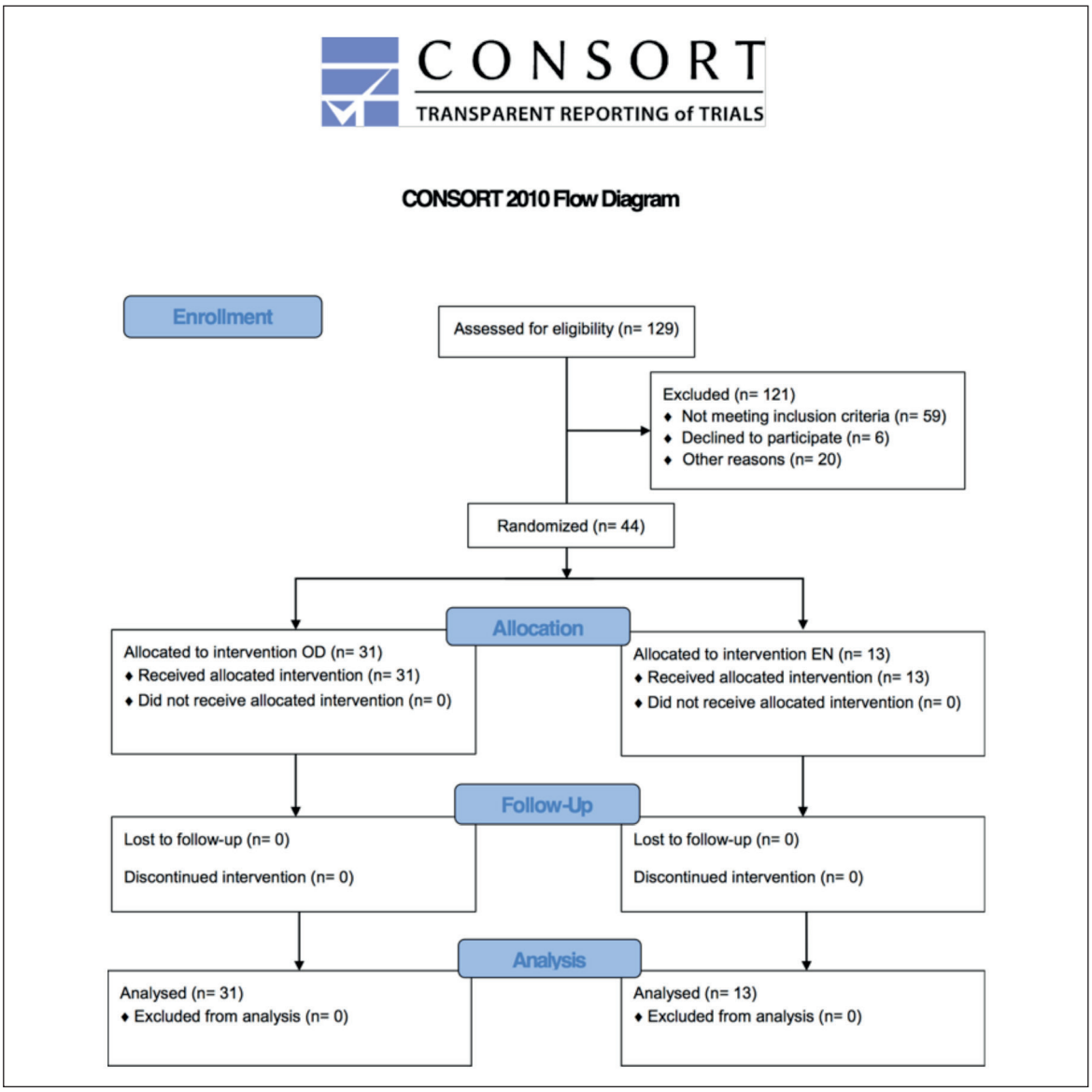

Figure 1. Study design and flowchart.

Plasma glucose concentrations were measured with an automated glucose analyzer (COBAS INTEGRA 400, Roche Diagnostics, Indianapolis, IN, USA); standard enzymatic colorimetric techniques (Roche143 Modular P800, Roche Diagnostics, Indianapolis, IN, USA) were used to determine serum lipid profile components. All the biochemical analyses were performed at the General Hospital Tor Vergata Foundation.

Body Composition Assessment

Body weight (kg) was measured to the nearest 0.1 kg, using a technical balance (Invernizzi, Rome, Italy). Height (m) was measured to the nearest 0.1 cm using a stadiometer (Invernizzi, Rome, Italy). BMI was calculated using the formula: BMI = body weight/height2 (kg/m^2). Body composition analysis was assessed by the BIA phase sensitive system (BIA 101S, Akern/RJL Systems, Florence, Italy).

Hand Grip Strength Analysis

An electronic dynamometer was used for the strength evaluation (DynEx, Akern, Florence, Italy), which was performed according to Shechtman et al[20] instructions. Subjects were instructed to maintain their position during the grip strength test.

Table I. Nutritional characteristics of Oral Diet (OD), Enteral Standard Nutrition (ESN), and Enteral Immunonutrition (EIN).

	OD	ESN	EIN
Calories (kcal)	2448.54	1532.00	1515.00
KJoule (kj)	10244.65	6432.00	6405.00
Proteins (g)	105.82	100.00	84.00
Carbohydrates (g)	328.62	162.00	201.00
Simple sugars (g)	113.19	26.00	6.00
Fats (g)	88.11	50.00	42.00
Fibers (g)	32.39	14.00	0.00
Saturated fatty acids (g)	30.98	27.00	24.00
Unsaturated fatty acids (g)	8.60	13.40	8.70
Mono unsaturated fatty acids (g)	42.89	8.00	8.85
Vitamin B1 (mg)	1.21	1.92	1.80
Vitamin B2 (mg)	2.55	2.20	2.55
Niacin (mg)	20.32	28.00	24.00
Pantenotenic acid (mg)	3.04	7.60	12.00
Vitamin B6 (mg)	2.16	2.52	2.25
Folic Acid (µg)	499.15	400.00	300.00
Vitamin B12 (µg)	4.50	5.60	6.00
Vitamin C (µg)	268.15	180.00	100.50
Biotin (µg)	83.17	90.00	105.00
Vitamin A (µg)	2227.56	1300.00	1500.00
Vitamin D (µg)	0.73	18.00	10.05
Vitamin E (mg)	18.56	26.00	45.00
Vitamin K (µg)	263.91	80.00	100.50
Sodium (mg)	1790.82	1440.00	1605.00
Potassium (mg)	4377.50	2800.00	2010.00
Iron (mg)	13.92	18.00	18.00
Calcium (mg)	1363.77	1060.00	1200.00
Phosphorous (mg)	1785.28	900.00	1080.00
Copper (mg)	2.58	2400.00	2.55
Magnesium (mg)	398.25	300.00	345.00
Manganese (mg)	2.84	3.20	3.00
Zinc (mg)	14.13	14.00	22.50
Selenium (µg)	26.71	106.00	70.50
Chrome (µg)	102.18	180.00	150.00
Iodium (µg)	107.50	220.00	225.00
Chloride (mg)	1418.89	1640.00	1800.00
Fluoride (mg)	0.25	2.20	2.55
Water (g)	1434.55	1634.00	0.00
Arginine (g)	4.64	0.00	19.50
Glutamine	22.31	20.00	0.00
Omega 3 (g)	0.80	0.00	4.95
MCT (g)		18.00	9.15
Molybdenum (µg)		200.00	240.00
Coline (mg)		600.00	405.00
Nucleic acids (g)		0.00	1.95
Osmolarity (mOsm/l)		286.00	298.00

Descriptive characteristics of the three nutritional interventions/formulations. Oral Diet (OD), Enteral Standard Nutrition (ESN) and Enteral Immunonutrition (EIN). Medium Chain Triglycerides (MCT).

Three repetitions were performed successively by the right hand and only then by the left hand. There was a 30-second rest period between each of the three repeated trials and a two-minute rest period between each hand.

Statistical Analysis

After the Shapiro-Wilk test, Mann-Whitney was performed to evaluate differences between nutritional interventions, or a nonparametric Wilcoxon tests were performed to evaluate the differences before and after nutritional interventions. All tests were considered significant at $p \leq 0.05$. Statistical analysis was carried out using IBM SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Of the 129 subjects enrolled, eighty-five subjects were excluded from the trial as follows: fifty-nine subjects did not meet the inclusion criteria; six subjects declined to participate; twenty subjects were excluded for other reasons. Finally, forty-four patients completed the study (Figure 1). No changes to trial outcomes after the trial start occurred. The average age of subjects was 65.48 ± 12.66 years, 23.3% females and 76.7% males. Descriptive characteristics of the study subjects were reported in Table II.

In blood sample analyses, we observed some significant differences between the OD and EN groups for each time of intervention. At baseline, no differences between groups were highlighted ($p \geq 0.05$) (Table 3). On the contrary, at the 3rd and the 8th day of treatment, triglycerides were remarkably higher in the OD group (respectively, $p=0.028$ and $p=0.033$) compared to EN. At 8th day pre-albumin values were markedly higher in the EN group ($p=0.048$) (Table III). Furthermore, at 8th day bioelectrical data showed a significant increase of the phase angle (PA) values in the EN group compared to OD ($p=0.045$) (Table III).

Within OD treatment, we observed a significant reduction only of creatinine values between the 1st and 3rd day ($p=0.044$, $\Delta\%= -14.06\%$). No other changes were highlighted in the OD group ($p \geq 0.05$) (Table IV).

At the same time, between the 1st and 3rd day, ESN determined a significant increase of lymphocytes ($p=0.041$, $\Delta\%=43.94\%$) and a substantial decrease of glycemia ($p=0.032$, $\Delta\%=-15.35\%$). Between day 3 and day 8 EIN treatment caused a significant increase of pre-albumin ($p=0.048$, $\Delta\%=7.93\%$) and transferrin ($p=0.043$, $\Delta\%=44.52\%$) concentrations, as well for PA values ($p=0.042$, $\Delta\%=12.71\%$). No other changes were highlighted after EIN treatment ($p \geq 0.05$) (Table IV).

Table II. Descriptive characteristics at baseline of the study population.

	Overall (n= 44)
Weight (kg)	59.40 (46.00; 74.00)
BMI (kg/m^2)	20.00 (16.04; 28.38)
Hand Grip (kg)	20.15 (3.10; 37.40)
Phase Angle (°)	4.20 (2.10; 7.50)
UCR (ml/min(kg)	606.50 (425.30; 1390.00)
Leukocyte (10^3/ml)	8.02 (2.00; 22.00)
Platelets (10^3/ml)	199.50 (58.00; 481.00)
Neutrophils (10^3/ml)	5.81 (1.10; 25.34)
Lymphocytes (10^3/ml)	1.22 (0.37; 2.85)
Creatinine (mg/dl)	0.81 (0.17; 1.97)
Triglycerides (mg/dl)	123.00 (73.00; 315.00)
AST (UI/l)	18.00 (4.00; 363.00)
ALT (UI/l)	18.00 (7.00; 167.00)
Glycemia (mg/dl)	97.00 (71.00; 198.00)
Sodium (mEq/l)	138.00 (129.00; 145.00)
Potassium (mEq/l)	4.10 (2.10; 5.10)
Phosphoremia (mg/dl)	2.90 (1.30; 4.20)
Magnesemia (mEq/l)	2.09 (1.39; 3.60)
Calcium (mg/dL)	8.40 (7.00; 10.00)
Albumin (g/l)	2.60 (1.60; 3.50)
Pre-Albumin (mg/l)	10.80 (3.00; 17.00)
RBP (mg/dl)	2.00 (1.00; 3.00)
Transferrin (mg/dL)	162.00 (107.20; 200.00)
CRP (mg/dl)	52.47 (8.00; 70.65)

Descriptive characteristics of the three nutritional interventions. Oral Diet (OD), Enteral Standard Nutrition (ESN) and Enteral Immunonutrition (EIN). Medium Chain Triglycerides (MCT).

Discussion

The heterogeneous group of head and neck cancer (HNC) provides several onset sites, histopathological differences and, therefore, many possible treatments. The incidence/mortality rates of HNC, according to the 2012 GLOBOCAN report, were 14.3/7.9 for males and 4.4/2.2 for females worldwide[21]. Most of these cancers are HNSCC, and this type of cancer is typically related to tobacco and alcohol abuse, infection of human papillomavirus (HPV) family or some human herpes viruses.

Table III. Main nutritional risk screening tools for hospitalized children.

	Day 0			Day 3			Day 8		
	OD	EN		OD	ESN		OD	EIN	
No.	31	13	*p*	31	13	*p*	31	13	*p*
Weight (kg)	56.00 (46.00; 72.50)	60.00 (58.00; 74.00)	*0.294*	56.00 (49.00; 73.00)	60.30 (58.00; 75.50)	*0.352*	55.00 (48.00; 70.00)	60.20 (58.00; 73.2)	*0.375*
BMI (kg/m^2)	19.41 (16.04; 28.38)	21.91 (19.60; 25.73)	*0.485*	19.50 (16.15; 28.50)	21.91 (19.60; 25.20)	*0.165*	19.60 (16.80; 28.39)	22.99 (20.50; 24.50)	*0.188*
Hand Grip (kg)	20.15 (12.40; 31.20)	18.95 (3.10; 37.40)	*0.246*	19.70 (14.10; 32.70)	17.25 (5.70; 33.00)	*0.286*	17.25 (13.90; 34.50)	20.40 (5.90.6; 35.20)	*0.781*
Phase Angle (°)	4.00 (2.10; 7.50)	4.65 (2.70; 6.00)	*0.060*	4.10 (2.30; 7.60)	4.50 (2.70; 6.00)	*0.302*	4.05 (2.30; 7.60)	4.80 (4.50; 6.20)	*0.045**
UCR (ml/min(kg)	615.00 (425.30; 829.50)	598.00 (538.00; 1390.00)	*0.211*	525.80 (411.00; 1257.00)	611.65 (535.00; 881.00)	*0.083*	520.60 (400.00; 1020.00)	657.00 (599.00; 823.40)	*0.135*
Leukocyte (10^3/ml)	8.26 (2.00; 22.00)	7.60 (3.00; 16.00)	*0.744*	8.00 (2.57; 22.06)	5.52 (3.29; 15.51)	*0.477*	8.00 (2.57; 22.06)	6.16 (3.71; 10.20)	*0.587*
Platelets (10^3/ml)	190.00 (58.00; 481.00)	244.00 (127.00; 323.00)	*0.256*	236.00 (62.00; 481.00)	249.00 (113.00; 416.00)	*0.519*	300.00 (59.00; 469.00)	322.00 (176.00; 535.00)	*0.889*
Neutrophils (10^3/ml)	5.39 (1.10; 25.34)	6.25 (1.27; 11.53)	*0.517*	4.31 (0.99; 20.06)	3.77 (2.23; 11.41)	*0.907*	4.47 (1.57; 28.80)	4.46 (2.09; 6.11)	*0.456*
Lymphocytes (10^3/ml)	1.21 (0.37; 2.85)	1.26 (0.64; 1.81)[a]	*0.855*	1.32 (0.00; 3.00)	1.59 (1.00; 3.00)	*0.492*	1.50 (0.97; 1.89)	1.21 (0.76; 2.96)	*0.368*
Creatinine (mg/dl)	0.8 (0.17; 1,11)	0.87 (0.34; 1.97)	*0.355*	0.72 (0.24; 1.20)	0.83 (0.48; 2.38)	*0.170*	0.67 (0.36; 0.90)	0.77 (0.50; 2.40)	*0.291*
Triglycerides (mg/dl)	130.00 (104.00; 315.00)	114.00 (73.00; 168.00)	*0.668*	147.00 (106.00; 331.00)	109.50 (66.00; 193.00)	*0.028**	150.00 (102.00; 310.00)	105.50 (62.00; 134.00)	*0.033**
AST (UI/l)	19.00 (4.00; 363.00)	13.50 (7.00; 33.00)	*0.095*	17.00 (7.00; 42.00)	21.00 (4.00; 70.00)	*0.755*	20.50 (5.00; 72.00)	19.00 (12.00; 27.00)	*0.848*

Continued

Table III (Continued). Main nutritional risk screening tools for hospitalized children.

	Day 0			Day 3			Day 8		
	OD	EN		OD	ESN		OD	EIN	
No.	31	13	*p*	31	13	*p*	31	13	*p*
ALT (UI/l)	18.50 (9.00; 167.00)	15.50 (7.00; 35.00)	*0.265*	29.50 (11.00; 62.00)	19.50 (10.00; 90.00)	*0.460*	31.00 (13.00; 72.00)	18.00 (9.00; 53.00)	*0.577*
Glycemia (mg/dl)	91.00 (71.00; 198.00)	119.00 (91.00; 154.00)	*0.059*	93.00 (67.00; 134.00)	91.00 (73.00; 138.00)	*0.877*	82.00 (77.00; 130.00)	104.00 (78.00; 127.00)	*0.225*
Sodium (mEq/l)	138.00 (129.00; 145.00)	138.00 (133.00; 145.00)	*0.811*	138.50 (129.00; 144.00)	138.00 (120.00; 144.00)	*0.313*	140.00 (137.00; 142.00)	138.00 (132.00; 141.00)	*0.256*
Potassium (mEq/l)	4.10 (2.10; 5.10)	4.10 (3.10; 4.80)	*0.275*	3.65 (2.40; 4.50)	4.00 (3.30; 5.40)	*0.073*	3.80 (3.60; 5.10)	4.20 (3.70; 4.70)	*0.347*
Phosphoremia (mg/dl)	2.90 (1.30; 4.20)	2.80 (2.30; 3.60)	*0.688*	3.00 (1.20; 3.80)	2.90 (2.50; 3.20)	*0.899*	2.35 (0.50; 3.10)	3.30 (2.90; 3.30)	*0.107*
Magnesemia (mEq/l)	2.05 (1.39; 3.29)	2.18 (1.96; 3.60)	*0.189*	2.00 (1.40; 2.40)	2.10 (1.89; 3.90)	*0.178*	1.85 (1.20;2.60)	2.02 (1.72; 2.50)	*0.468*
Calcium (mg/dL)	8.40 (7.00; 10.00)	8.40 (7.00; 9.00)	*0.946*	8.15 (6.70; 9.30)	8.60 (7.70; 9.30)	*0.137*	7.85 (7.30; 8.50)	8.90 (7.50; 9.40)	*0.076*
Albumin (g/l)	2.30 (1.60; 3.50)	2.70 (2.20; 3.20)	*0.245*	2.35 (1.90; 3.70)	2.80 (2.00; 3.30)	*0.106*	2.40 (2.10; 4.10)	2.70 (2.50; 3.30)	*0.898*
Pre-Albumin (mg/l)	10.90 (3.00; 17.00)	10.25 (7.67; 14.10)	*0.600*	11.85 (2.50; 19.00)	10.50 (8.90; 13.60)	*0.580*	11.65 (3.00; 22.00)	15.00 (9.00; 22.20)	*0.048**
RBP (mg/dl)	2.16 (1.20; 3.00)	1.98 (1.00; 3.00)	*0.971*	2.10 (1.20; 3.08)	2.68 (1.00; 3.50)	*0.574*	2.20 (1.30; 3.30)	3.71 (1.53; 4.10)	*0.050*
Transferrin (mg/dL)	168.20 (108.20; 200.00)	158.40 (107.20; 200.00)	*0.125*	169.00 (110.00; 230.00)	161.00 (112.10; 238.00)	0.321	170.00 (109.00; 278.00)	200.25 (125.25; 245.00)	*0.050*
PCR (mg/dl)	28.50 (8.00; 59.00)	58.43 (15.00; 70.65)	*0.971*	27.84 (7.57; 60.68)	61.02 (19.00; 74.00)	*0.217*	24.54 (3.81; 49.93)	31.18 (8.00; 42.00)	*0.066*

Differences among Oral Diet (OD) and Enteral Standard Nutrition (ESN) or Enteral Immunonutrition (EIN) at day 0, 3 and 8. All parameters are presented as median, minimum and maximum, and were compared by Mann-Whitney test among type of nutrition support at day 0, 3 and 8. Statistical significance was attributed as $p<0.05$ (*). Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Retinol Binding Protein (RBP), C-Reactive Protein (CRP), Urinary Creatinine (UCR).

Table IV. Differences of Oral Diet (OD) or Enteral Nutrition (EN) treatments among hospitalization time.

	OD (n 31)			EN (n 13)		
	Day 0	Day 3	Day 8	Day 0	Day 3	Day 8
Weight (kg)	56.00 (46.00; 72.50)	56.00 (49.00; 73.00)	55.00 (48.00; 70.00)	60.00 (58.00; 74.00)	60.30 (58.00; 75.50)	60.20 (58.00; 73.2)
BMI (kg/m^2)	19.41 (16.04; 28.38)	19.50 (16.15; 28.50)	19.60 (16.80; 28.39	21.91 (19.60; 25.73)	21.91 (19.60; 25.20)	22.99 (20.50; 24.50)
Hand Grip (kg)	20.15 (12.40; 31.20)	19.70 (14.10; 32.70)	7.25 1(13.90; 34.50)	18.95 (3.10; 37.40)	17.25 (5.70; 33.00)	20.40 (5.90.60; 35.20)
Phase Angle (°)	4.00 (2.10; 7.50)	4.10 (2.30; 7.60)	4.05 (2.30; 7.60)	4.65 (2.70; 6.00)	4.50 (2.70; 6.00)[b]	4.80 (4.50; 6.20)[b]
UCR (ml/min (kg)	615.00 (425.30; 829.50)	525.80 (411.00; 1257.00)	520.60 (400.00; 1020.00)	598.00 (538.00; 1390.00)	611.65 (535.00; 881.00)	657.00 (599.00; 823.40)
Leukocytes (10^3/ml)	8.26 (2.00; 22.00)	8.00 (2.57; 22.06)	8.00 (2.57; 22.06)	7.60 (3.00; 16.00)	5.52 (3.29; 15.51)	6.16 (3.71; 10.20)
Platelets (10^3/ml)	190.00 (58.00; 481.00)	236.00 (62.00; 481.00)	300.00 (59.00; 469.00)	244.00 (127.00; 323.00)	249.00 (113.00; 416.00)	322.00 (176.00; 535.00)
Neutrophils (10^3/ml)	5.39 (1.10; 25.34)	4.31 (0.99; 20.06)	4.47 (1.57; 28.80)	6.25 (1.27; 11.53)	3.77 (2.23; 11.41)	4.46 (2.09; 6.11)
Lymphocytes (10^3/ml)	1.21 (0.37; 2.85)	1.32 (0.00; 3.00)	1.50 (0.97; 1.89)	1.26 (0.64; 1.81)[a]	1.59 (1.00; 3.00)[a]	1.21 (0.76; 2.96)
Creatinine (mg/dl)	0.8 (0.17; 1,11)[a]	0.72 (0.24; 1.20)[a]	0.67 (0.36; 0.90)	0.87 (0.34; 1.97)	0.83 (0.48; 2.38)	0.77 (0.50; 2.40)
Triglycerides (mg/dl)	130.00 (104.00; 315.00)	147.00 (106.00; 331.00)	150.00 (102.00; 310.00)	114.00 (73.00; 168.00)	109.50 (66.00; 193.00)	105.50 (62.00; 134.00)
AST (UI/l)	19.00 (4.00; 363.00)	17.00 (7.00; 42.00)	20.50 (5.00; 72.00)	13.50 (7.00; 33.00)	21.00 (4.00; 70.00)	19.00 (12.00; 27.00)
ALT (UI/l)	18.50 (9.00; 167.00)	29.50 (11.00; 62.00)	31.00 (13.00; 72.00)	15.50 (7.00; 35.00)	19.50 (10.00; 90.00)	18.00 (9.00; 53.00)
Glycemia (mg/dl)	91.00 (71.00; 198.00)	93.00 (67.00; 134.00)	82.00 (77.00; 130.00)	119.00 (91.00; 154.00)[a]	91.00 (73.00; 138.00)[a]	104.00 (78.00; 127.00)
Sodium (mEq/l)	138.00 (129.00; 145.00)	138.50 (129.00; 144.00)	140.00 (137.00; 142.00)	138.00 (133.00; 145.00)	138.00 (120.00; 144.00)	138.00 (132.00; 141.00)
Potassium (mEq/l)	4.10 (2.10; 5.10)	3.65 (2.40; 4.50)	3.80 (3.60; 5.10)	4.10 (3.10; 4.80)	4.00 (3.30; 5.40)	4.20 (3.70; 4.70)
Phosphoremia (mg/dl)	2.90 (1.30; 4.20)	3.00 (1.20; 3.80)	2.35 (0.50; 3.10)	2.80 (2.30; 3.60)	2.90 (2.50; 3.20)	3.30 (2.90; 3.30)
Magnesemia (mEq/l)	2.05 (1.39; 3.29)	2.00 (1.40; 2.40)	1.85 (1.20;2.60)	2.18 (1.96; 3.60)	2.10 (1.89; 3.90)	2.02 (1.72; 2.50)
Calcium (mg/dL)	8.40 (7.00; 10.00)	8.15 (6.70; 9.30)	7.85 (7.30; 8.50)	8.40 (7.00; 9.00)	8.60 (7.70; 9.30)	8.90 (7.50; 9.40)
Albumin (g/l)	2.30 (1.60; 3.50)	2.35 (1.90; 3.70)	2.40 (2.10; 4.10)	2.70 (2.20; 3.20)	2.80 (2.00; 3.30)	2.70 (2.50; 3.30)
Pre-Albumin (mg/l)	10.90 (3.00; 17.00)	11.85 (2.50; 19.00)	11.65 (3.00; 22.00)	10.25 (7.67; 14.10)	10.50 (8.90; 13.60)[b]	15.00 (9.00; 22.20)[b]
RBP (mg/dl)	2.16 (1.20; 3.00)	2.10 (1.20; 3.08)	2.20 (1.30; 3.30)	1.98 (1.00; 3.00)[b]	2.68 (1.00; 3.50)	3.71 (1.53; 4.10)[b]
Transferrin (mg/dL)	168.20 (108.20; 200.00)	169.00 (110.00; 230.00)	170.00 (109.00; 278.00)	158.40 (107.20; 200.00)	161.00 (112.10; 238.00)[b]	200.25 (125.25; 245.00)[b]
PCR (mg/dl)	28.50 (8.00; 59.00)	27.84 (7.57; 60.68)	24.54 (3.81; 49.93)	58.43 (15.00; 70.65)	61.02 (19.00; 74.00)	31.18 (8.00; 42.00)

Differences of Oral Diet (OD) or Enteral Nutrition (EN) treatments among hospitalization time. All parameters are presented as median, minimum and maximum, and were compared by Wilcoxon test between day 0 *vs.* day 3 (a), day 3 *vs.* day 8 (b), day 0 *vs.* day 8 (c) according to OD treatment, or day 0 *vs.* day 3 (a) and day 3 *vs.* day 8 (b) according to EN support. Statistical significance was attributed as $p<0.05$ (a,b,c).

HNC treatment usually includes surgery, radiotherapy or systemic therapy. Although radiotherapy and chemotherapy are becoming increasingly adopted as organ preservation treatments, surgery represents the main treatment for HNC[22]. However, a defection of immune function, with consequent infections, is strongly associated with cancer surgery, increasing postoperative mortality and morbidity. To reduce these complications, immunonutrition is highly recommended. The role of perioperative immunonutrition is to induce an immune response and protein synthesis, and, at the same time, reduce inflammation provoked by surgical interventions[23,24].

This particular type of artificial nutrition is usually enriched with specific amino acids like glutamine and arginine, nucleotides, vitamins and pro-vitamins with antioxidant proprieties (i.e., vitamin A, E, C, β-carotene), zinc, selenium and omega-3. Major surgery interventions could lead to a worse nutritional status, which is usually already compromised before the hospitalization[25]. According to many nutritional societies' guidelines, enteral immunonutrition is recommended for 5 or 7 days in pre-operative time. Malnourished or non-malnourished patients, instead, continuing immunonutrition can be administrated in post-operative time in malnourished patients for 5 to 7 days or until oral feeding has been restored[26,27].

In this context, the immunonutrition therapy and the assessment of nutritional status through BIA analysis should be considered fundamental for the nutritional outcome and prognosis of cancer patients.

During the last decade, BIA acquired more and more importance in the prediction of the outcome of therapy in cancer patients. Tumor products, as well as pro-inflammatory cytokines, can alter cell mass and membrane integrity, a condition that can lead to surgical and life-threatening complications. PA, which derives from the values of resistance and reactance, represents a marker of cellular function and it is a significant predictor of survival in advanced cancer condition, as well the best predictive clinical factor in the evaluation of muscle strength, quality of life and mortality in cancer patients[9,10,28]. The severity of the disease and the degree of malnutrition in cancer patients highly correlate with PA. Previous studies reported a significant difference in PA values among healthy control, cancer patients and cancer patients after surgical intervention, highlighting how malignancy and treatment affect cell membranes and tissue interfaces in cancer patients[27]. However, in cancer patients, the variability of PA is wide, according to the localization and the stage of the tumor, as well the hydration status. It was observed that well-nourished newly diagnosed HNC patients have higher PA than malnourished patients[29,30]. In advanced HNC, PA might be a predictor of survival alone or in comparison with other prognostic factors[31]. In this work, EIN treatment increases PA, reflecting the improvement of nutritional, inflammatory and clinical status. EIN treatment leads to the rise of PA for the modulation of immune response and the reduction of inflammatory state and cellular stress, improving clinical conditions and decreasing the risk of medical complications[10]. According to the previous literature[32], our results suggested an improvement of nutritional blood parameters after EIN treatment, especially for prealbumin and transferrin compared to OD treatment. Serum protein concentrations are influenced by several adding factors, like inflammation, which provides the release of several cytokines and acute phase products inhibiting albumin, prealbumin, and transferrin synthesis[33].

A cancer pro-inflammatory state increases energy-protein expenditure and leads the development of malnutrition. This involves a depletion of energy, protein and functional reserves, exposing the subject to an increased death risk[34]. Thus, the improvement of prealbumin and transferrin could be due to the high content of omega-3 fatty acids contained in EIN, which exert strong and inflammatory properties, decreasing pro-inflammatory cytokine levels[35,36] as well as nucleotides, which have anti-inflammatory capabilities through the down-regulation of tumor necrosis factor-alpha (TNF-α)[37].

Furthermore, the observation of metabolic markers highlighted a reduction of glycemia after 3 days of ESN treatment, probably due to a reduction of carbohydrate intake. In the first three days of OD treatment, we observed a reduction of creatinine levels due to an improvement of hydration during the hospitalization. Moreover, comparing the outcomes at day 3 and 8, OD showed higher triglycerides than EN treatments. These results could be attributable to the different composition of dietetic treatment.

After ESN treatment, we observed an improvement of lymphocyte count. Total lymphocyte count is a measure of nutritional status. In fact, under 2.000 cells/mm^3 values, it is possible to define mild, moderate and severe malnutrition. The improvement of lymphocyte count could be due to energy supplementation, in patients unable to feed,

which is sufficient to restore physiologic processes, including immune function[38]. Furthermore, after EIN treatment, we observed physiological maintenance of lymphocyte response, probably due to arginine[39], nucleotides and MCT, according to the previous results[40]. Nucleotides free diets have demonstrated a significant reduction of the immune response, because MCTs are able to stimulate lymphocyte differentiation, proliferation, activation and function[38], while MCTs can modulate the inflammatory and immune response, promoting a better patient outcome in many ways[41].

Conclusions

At the best of our knowledge, this is the first study that investigates the early change of PA values related to the improvement of nutritional markers with an immunonutrition treatment. Immunonutrition is recognized as supportive care to anti-cancer drug therapies. We suggest the relationship between immunonutrition therapy and the improvement of nutritional and anti-inflammatory markers[42-44], as well as PA, an indicator of cellular function and predictor of survival in cancer patients, becoming increasingly important in cancer therapy. Although the variability of PA is wide in cancer patients, its use over the time could represent a useful marker for the longitudinal observations in individual health changes, during or after the disease progression. This study was not without limitations, as the limited sample size. However, our results suggest that malnourished subjects affected by HNSCC could find major health benefits from immunonutrition. Our data should be confirmed on a larger number of subjects, with a prospective interventional clinical trial.

Author Contributions

L.D.R. designed the research, discussed the results and wrote the paper; G.C. analyzed the data and wrote the paper; G.C. conducted the research and collected the data; L.R. analyzed the data and contributed to the discussion of results; L.S., M.C.M, G.M. contributed to the discussion of the results; A.D.L. contributed to the discussion of the results and had primary responsibility for the final content. All authors read and approved the submitted and the final version of the manuscript. All the authors agree to be personally accountable for the author's contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

Acknowledgments

We are indebted to all the subjects in the study. We thank Prof Stefano Di Girolamo, Prof Riccardo Santoni, Prof Mario Roselli and their team, We also thank the entire medical team from the Section of Clinical Nutrition and Nutrigenomic, University of Rome Tor Vergata, for their technical assistance in conducting the clinical aspects of this study.

Declaration of funding interests

This study did not receive any research funding or sponsorship. The founding sponsors had no role in the design of the study, the collection, analyses, or interpretation of data, the writing of the manuscript and the decision to publish the results.

Conflict of Interests

The authors declare that they have no conflict of interest.

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